

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Article 36 and Rule 70)


REC'D 24 JAN 2006

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Applicant's or agent's file reference 50375C:MOB	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. CT/AU2004/001368	International filing date (day/month/year) 7 October 2004	Priority date (day/month/year) 7 October 2003
International Patent Classification (IPC) or national classification and IPC Int. Cl. C07D 207/34 (2006.01) (continued in supplemental box)		
Applicant UNIVERSITY OF WESTERN SYDNEY et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
- a. ☒ (sent to the applicant and to the International Bureau) a total of 32 sheets, as follows:
- ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
- ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
- b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
- | | |
|--|---|
| <input checked="" type="checkbox"/> Box No. I | Basis of the report |
| <input type="checkbox"/> Box No. II | Priority |
| <input type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application |

Date of submission of the demand 21 March 2005	Date of completion of this report 10 January 2006 10 January 2006 10 January 2006 11 January 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer  O.L. CHAI Telephone No. (02) 6283 2482

Box No. I Basis of the report

With regard to the language, this report is based on:

☒ The international application in the language in which it was filed

☐ A translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3(a) and 23.1 (b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages 1-61 as originally filed/furnished

pages* 62-65 received by this Authority on 20 July 2005 with the letter of 19 July 2005

pages* received by this Authority on with the letter of

☒ the claims:

pages as originally filed/furnished

pages* as amended (together with any statement) under Article 19

pages* 66, 67, 69, 70, 72 received by this Authority on 20 July 2005 with the letter of 20 July 2005

pages* 68, 71, 73, 74 received by this Authority on 23 December 2005 with the letter of 23 December 2005

☒ the drawings:

pages as originally filed/furnished

pages 1/19-19/19 received by this Authority on 14 December 2004 with the letter of 14 December 2004

pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/figs

☐ the sequence listing (*specify*):

☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/figs

☐ the sequence listing (*specify*):

☐ any table(s) related to the sequence listing (*specify*):

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001368

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Statement

Novelty (N)	Claims 1-19	YES
	Claims	NO
Inventive step (IS)	Claims 1-19	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-19	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

- D1 WO 1998/049142
- D2 WO 2003/041128
- D3 US 4942227
- D4 WO 1999/062551
- D5 WO 2003/020877
- D6 Arzneimittel-Forschung (2003), 53(2), 107-113
- D7 Bioorganic & Medicinal Chemistry (2002), 10(10), 3313-3318
- D8 Nucleic Acids Research (2000), 28(24), 4856-4864
- D9 European Journal of Biochemistry (1999), 266(2), 392-402
- D10 Journal of the American Chemical Society (1999), 121(6), 1113-1120
- D11 Medicinal Chemistry Research (1996), 6(6), 365-371
- D12 Tetrahedron (1994), 50(42), 12065-84
- D13 Bioorganic & Medicinal Chemistry Letters (1993), 3(8), 1751-6
- D14 Journal of the American Chemical Society (1987), 109(24), 7564-6

As a result of the amendments, none of the cited documents discloses or fairly suggests the invention as claimed. Therefore, claims 1-19 are considered to meet the requirements of Article 33(2)-(3) PCT with regard to novelty and inventive step.

Claims 1-19 are considered to meet the requirements of Article 33(4) of the PCT with regards to industrial applicability.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claims 1-12 and 16-19 are not fully supported by the description. The scope as defined by the said claims extends far beyond what has been disclosed in the description. From a fair reading of the specification, there is only substantial support for a small number of compounds – there are only 4 examples of the compounds claimed. The claims should be drafted to clearly reflect what has been disclosed.
2. Claims 1 and 9 are not clear in scope.
 - (i) The variables M^1 , M^2 and M^3 are merely defined by results, it is not clear what metal coordination complex can be included.
 - (ii) The variables T^1 , T^2 and T^3 have not been defined clearly except that it is a linker group. It is not clear what can be included.
 - (iii) The term “sequence selective” does not seem to have a clear definition and it is not clear what pyrrole imidazole polyamides fall within the scope and what are excluded.
3. Claim 7 is not fully supported by the description. The definition of the linker groups includes many linkers that the specification does not have any support for.
4. Claim 17 is not clear. It is not clear what can be included in the terms “therapeutic agent”, “reporter group” and “a sequence”. These imprecise terms render the scope unclear.
5. Claim 19 is not clear. It does not define clearly what the method of diagnosis actually diagnoses.

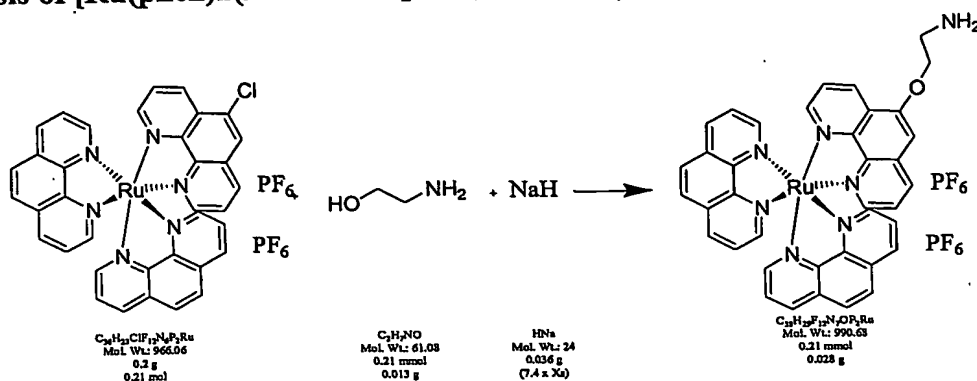
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

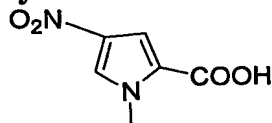
Continuation of: IPC Classification

Int. Cl.

<i>A61K 31/4164</i> (2006.01)	<i>A61P 31/18</i> (2006.01)	<i>C07D 233/90</i> (2006.01)
<i>A61K 31/40</i> (2006.01)	<i>A61P 35/00</i> (2006.01)	
<i>A61P 31/12</i> (2006.01)	<i>C07D 209/56</i> (2006.01)	

Synthesis of [Ru(phen)₂(Phen-4-NH₂-CH₂CH₂-NH₂)](PF₆)₂

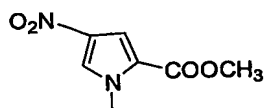
The ruthenium complex, [Ru(phen)₂4-Cl-Phen](PF₆)₂ (0.2 g, 0.21 mmol) was also suspended in deaerated DMF (5 mL) while separately NaH (0.036 g, 1.5 mmol) was also suspended in a stirring solution of dry, deaerated DMF (5 mL). Ethanolamine (12.8 μL, 0.21 mmol) was added to the solution of NaH. The two solutions were mixed via cannula and the resulting black solution heated at 40 °C for 2 hr. The solution was evaporated to dryness under reduced pressure leaving a red black residue which was purified by flash chromatography on silica gel, eluting with acetonitrile (5% saturated KNO₃ solution and 10 % water). Fractions containing unreacted starting complex and product were isolated by TLC (SiO₂, ACN/5% saturated KNO₃/10% H₂O). These fractions were combined, reduced to dryness then extracted into dichloromethane (4 x 100 mL) from H₂O (100 mL). The extracts were reduced to dryness and subsequently purified on a column of TLC grade silica gel (ACN/1% saturated KNO₃/10% H₂O). This purification achieved a separation of bands containing unreacted starting complex and product. The product (band 2) was collected, reduced to dryness then extracted into dichloromethane (4 x 100 mL) from H₂O (100 mL). Evaporation of the solution to dryness under reduced pressure gave the product as a deep red solid. ¹H NMR (CD₃CN): 8.54 (d, 4H), 8.44 (dd, 2H), 8.28 (d, 1H), 8.23 (s, 4H), 8.18 (d, 1H), 8.08 (d, 1H), 8.00 (d, 1H), 7.83 (d, 1H), 7.76 (d, 1H), 7.65 (bm, 4H), 7.40 (dd, 1H), 6.70 (d, 1H), 6.38 (d, 1H), 1.30 (bs, 4H).

1-Methyl-4-nitropyrrole-2-carboxylic acid

Acetic anhydride (20 mL) was treated with nitric acid (4.0 mL, 70%) and the mixture heated to 50 °C for 15 min then cooled to room temperature, and slowly added to a suspension of 1-methyl-2-pyrrolecarboxylic acid (4 g, 15.98 mmol) in Ac₂O (12 mL) cooled to -25 °C. The mixture was stirred at -15 °C for 0.5 hr, then the temperature

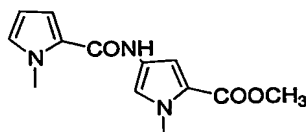
was allowed to rise to ambient, and stirring was continued for 20 min. The mixture was again cooled to -25 °C and the precipitate collected in a funnel cooled with dry ice, the solid was washed with a small quantity of cold Ac₂O (-25 °C). The crystalline solid was taken up in water containing NaOH (1 g). Acidification with the HCl precipitated the pure compound. NMR as previously reported.

Methyl 1-methyl-4nitropyrrole-2-carboxylate



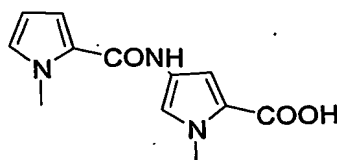
A cold solution of H₂SO₄ (2.9 mL) in MeOH (28.96 mL) was added to 1-methyl-4-nitropyrrole-2-carboxylic acid (2.897 g, 2.35 mmol). The mixture was refluxed for 24 hr. Water was added and the mixture extracted CHCl₃. The organic layer was dried (MgSO₄), and the solvent evaporated under vacuum to afford the creamy white product. NMR as previously reported.

Py/Py-COOCH₃



Methyl *N*-methyl-4-nitro pyrrole-2-carboxylate (0.5 g, 27.17 mmol) in MeOH (64 mL) and Pd/C (10%, 6 mg) was stirred under H₂ (1 atm) until the TLC showed no starting material (1 hr). The mixture was filtered through celite to remove the catalyst and DMF was added (3 mL). MeOH was removed under vacuum. *N*-methyl pyrrole-2-carboxylic acid (1.3 mol equiv) was added followed by HOBt (88 mg, 1.5 mol equiv), TBTU (209 mg, 1.5 equiv) and Et₃N (220 mg, 5 equiv). The solution was stirred for 1 hr at room temperature and the solvent removed under vacuum. The residue was purified by flash chromatography (100% DCM).

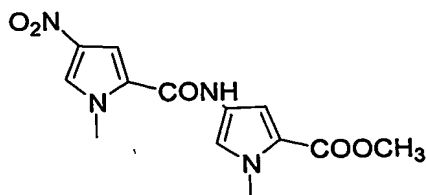
Py/Py-COOH



Py/Py-COOCH₃ (360 mg, 1.38 mmol) in THF/MeOH (1.1 / 7.5 mL) was added LiOH (1 M, 5.5 mL) and the solution stirred at 60 °C (oil bath) for 1.5 hr and monitored by TLC (10%, MeOH/CH₂Cl). The organics were evaporated under vacuum, the solution

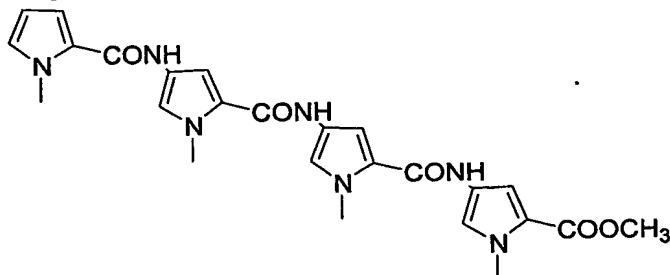
cooled and acidified with HCl (1 M 5mL). The solid was collected and air dried and left in a desiccator under vacuum overnight. NMR as previously reported.

NO₂-Py/Py-COOCH₃



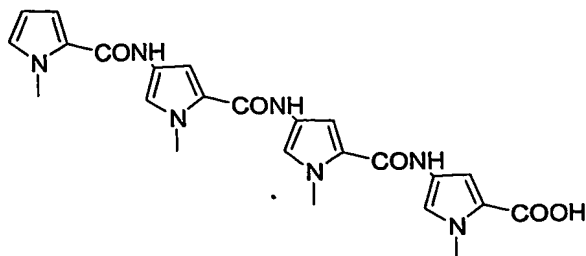
NO₂-Py-COOCH₃ (1.45 g, 7.83 mmol) in MeOH (150 mL) and Pd/C (174 mg) was stirred under H₂ (1 atm) for 1 hr. The mixture was filtered through celite and DMF (3 mL) added. MeOH was removed under vacuum. NO₂-Py-COOH (1.8 g,) was added followed by HOBT (255.2 mg, 1.89 mmol) and TBTU (606 mg, 1.89 mmol) and Et₃N (638 mg, 6.32 mmol). The solution was stirred for 1 hr at room temp and the solvent (DMF) removed under vacuum until a small quantity remained. The pure compound was precipitated by addition of MeOH. %). ¹H NMR (d-DMSO): 10.21 (s, 1H), 8.15 (d, 1H), 7.53 (d, 1H), 7.43 (d, 1H), 6.88 (d, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H).

Py/Py/Py/Py-COOCH₃



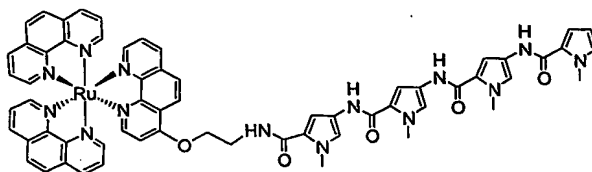
NO₂-Py/Py-COOCH₃ (213 mg, 0.69 mmol) was dissolved in DMF (25 mL) and added Pd/C catalyst (15 mg) and stirred under H₂ until the amine was formed. The mixture was filtered through celite and Py/Py-COOH (166 mg, 0.66 mmol) added to the solution followed by HOBT (22 mg, 0.16 mmol), TBTU (51 mg, 0.16 mmol) and Et₃N (53 mg, 0.52 mmol). The reaction was then left to couple for 1.5 hr. The DMF was removed under reduced pressure to yield the compound.

Py/Py/Py/Py-COOH



Py/Py/Py/Py-COOCH₃ (100 mg, 0.20 mmol) in DMF (10 mL) was added NaOH (0.75 mL) and the solution stirred at 60 °C for 1 hr. The organics were evaporated until approx. 3 mL remained and acidified with HCl (1 M, 5 mL) to yield the product.

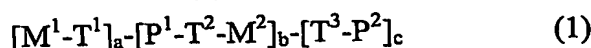
[Ru(phen)₂(phen-4-O-CH₂CH₂NHCO-Py/Py/Py/Py)](PF₆)₂



[Ru(phen)₂(phen-4-O-CH₂CH₂NH₂)](PF₆)₂ (28 mg, 0.03 mmol) dissolved in DMF (25 mL) and added Pd/C catalyst (15 mg) and stirred under H₂ until the amine was formed. The mixture was filtered through celite) and Py/Py/Py/Py-COOH (75 mg, 0.15 mmol) added to the solution followed by HOBT (22 mg, 0.16 mmol), TBTU (51 mg, 0.16 mmol) and Et₃N (53 mg, 0.52 mmol). The reaction was then left to couple for 2 hr. The DMF was removed under reduced pressure to yield the compound.

The claims defining the invention are as follows:

1. A compound of formula (1)



or a salt thereof,

wherein

M^1 and M^2 are the same or different and are each a metal coordination complex, wherein at least one of M^1 and M^2 is capable of interacting with a major groove or minor groove of a polynucleotide;

P^1 and P^2 are the same or different and are each a sequence selective pyrrole-imidazole polyamide;

T^1 , T^2 and T^3 are the same or different and are each a linker group;

a is 0, or 1;

b is an integer selected from 1, 2, 3, 4 and 5;

wherein when b is an integer greater than 1, each P^1 , each T^2 and each M^2 may be the same or different; and

c is 0, 1 or 2; wherein when c is 2, each P^2 may be the same or different and each T^3 may be the same or different.

2. A compound according to claim 1, $a = 0$, $b = 1$, and $c = 0$.

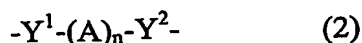
3. A compound according to claim 1, wherein M^1 and M^2 are the same or different and are individually selected from a platinum complex, a palladium complex, a ruthenium complex, and a rhodium complex.

4. A compound according to claim 1, wherein M^1 and M^2 are independently selected from $\text{cis-Pt}(\text{NH}_3)_2\text{Cl}$ and $\text{trans-Pt}(\text{NH}_3)_2\text{Cl}$.

5. A compound according to claim 1, wherein each pyrrole-imidazole polyamides (P^1 , P^2) independently comprises a plurality of heterocyclic rings selected from the group consisting of optionally substituted N-methylimidazole (Im), optionally substituted N-methylpyrrole (Py) and optionally substituted 3-hydroxy N-methylpyrrole (Hp).

6. A compound according to claim 5, wherein each pyrrole-imidazole polyamide independently comprises 3 heterocyclic rings or 4 heterocyclic rings.

7. A compound according to claim 1, wherein the linker groups (T^1 , T^2 , T^3) are the same or different and each has the formula (2):



wherein

Y^1 and Y^2 may be the same or different and are independently selected from NH, -NH₂, C=O, C=S, C=NH, O, OH, S, SH, S(O), S(O)₂, NR³, NHR³, N(R³)₂, an optionally substituted cycloalkylamine, an optionally substituted cycloalkyldiamine, and an optionally substituted heteroaryl group (e.g., an optionally substituted N-heteroaryl group such as pyridyl, phenanthrolyl, 2,2'-bipyridyl); where each R³ is independently selected from alkyl, cycloalkyl, aryl or heteroaryl;

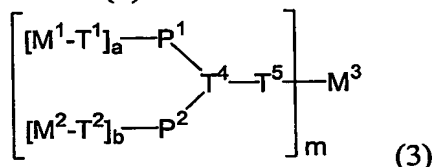
A is selected from an optionally substituted C₁₋₁₀ alkylene, an optionally substituted C₂₋₁₀ alkenylene, an optionally substituted C₂₋₁₀ alkynylene, an optionally substituted C₃₋₆ cycloalkylene, an optionally substituted C₆₋₁₀ aryl, C=O, C=S, and C=NH, NH, O, S, NH₂, OH, SH, S(O), S(O)₂, amino acids, and spermidine; and

n is an integer selected from 1 to 20,

wherein when n is an integer greater than 1, each (A) group may be the same or different.

8. A compound according to claim 7, wherein each linker group independently comprises a group selected from -NH-(CH₂)_n-NH₂-, -NH-CH₂CH₂CH₂-O-CH₂CH₂-O-CH₂CH₂-O-CH₂CH₂CH₂-NH₂-, -NH-C(O)-CH₂CH₂-NH-C(O)-CH₂CH₂CH₂NH₂-, -S-(CH₂)_n-O-(CH₂)_n-S-, or -NH-(CH₂)_n-O-, and -C(O)-NH-CH₂-C(O)-NH-CH(CH₂SH)-C(O)-NH-, where n is an integer from 1 to 20.

9. A compound of formula (3):



where

M¹, M², M³ are the same or different and are each a metal coordination complex as defined for M¹ and M² of formula (1) in claim 1, wherein at least one of M¹, M² and M³ is capable of interacting with a major groove or minor groove of a polynucleotide;

P¹ and P² are the same or different and are each a sequence selective pyrrole-imidazole polyamide as defined for formula (1) in claim 1;

T¹ and T² are the same or different and are each a linker group of formula (2) as defined for formula (1) in claim 1;

T⁵ is a linker group of formula (2) as defined for T¹ and T² of formula (1) in claim 1, wherein one of Y¹ and Y² is bound to a metal complex M³ and the other of Y¹ and Y² is covalently bound to T⁴;

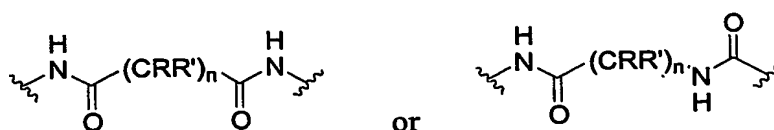
T^4 is a linker group of formula (2) as defined for T^1 and T^2 of formula (1) in claim 1, wherein Y^1 is covalently bound to a pyrrole-imidazole polyamide, Y^2 is covalently bound to a pyrrole-imidazole polyamide, and wherein one Y^1 , Y^2 and A is covalently bound to T^5 ;

a and b are independently selected from 0 and 1; and
m is 1, 2, 3 or 4.

10. A compound according to claim 9, wherein m is 1 or 2.

11. A compound according to claim 9, wherein a = 0, b = 1, and m = 1.

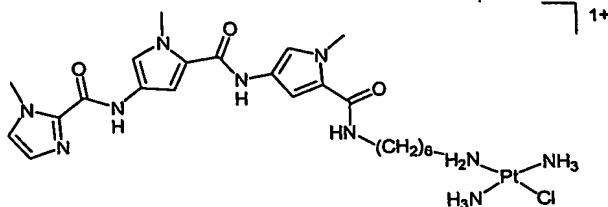
12. A compound according to claim 9, wherein T^4 comprises



wherein n is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10,
each (CRR') is independently an optionally substituted alkylene; and
wherein in one (CRR'), R' is absent and CR is covalently bound to T^5 .

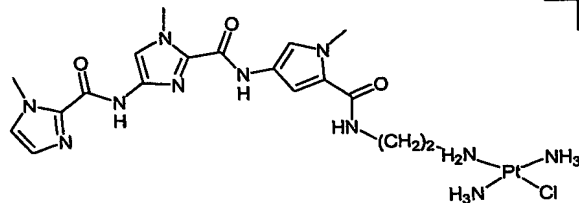
13. A compound according to claim 1, wherein said compound is selected from

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1+

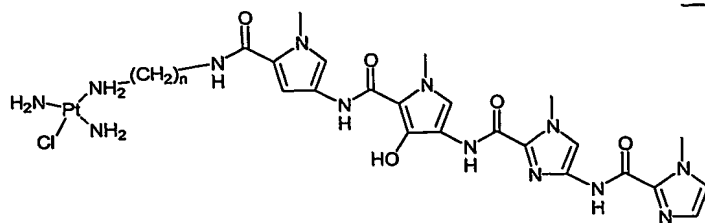
“trans-Im/Py/Py-[CONH(CH₂)₆-NH₂]Pt(NH₃)₂Cl”;



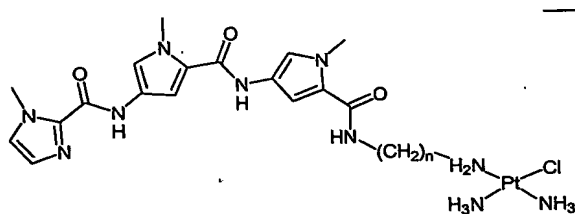
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“trans-Im/Py/Py-[CONH(CH₂)₂-NH₂]Pt(NH₃)₂Cl”;

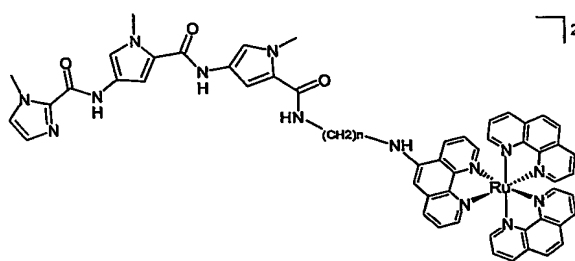
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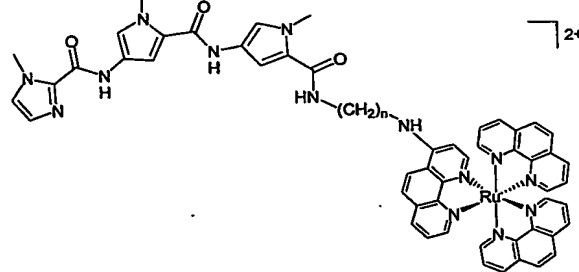
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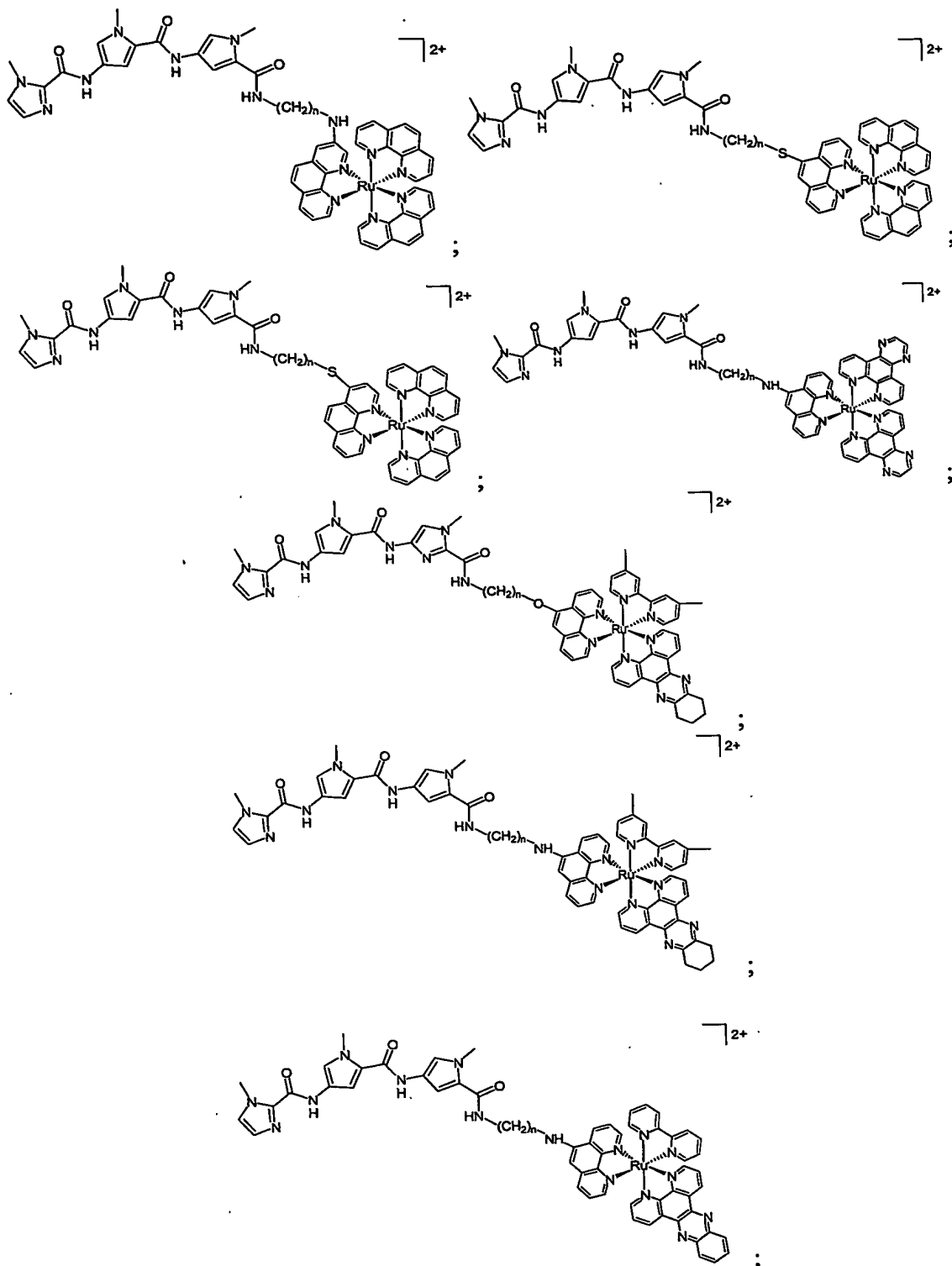
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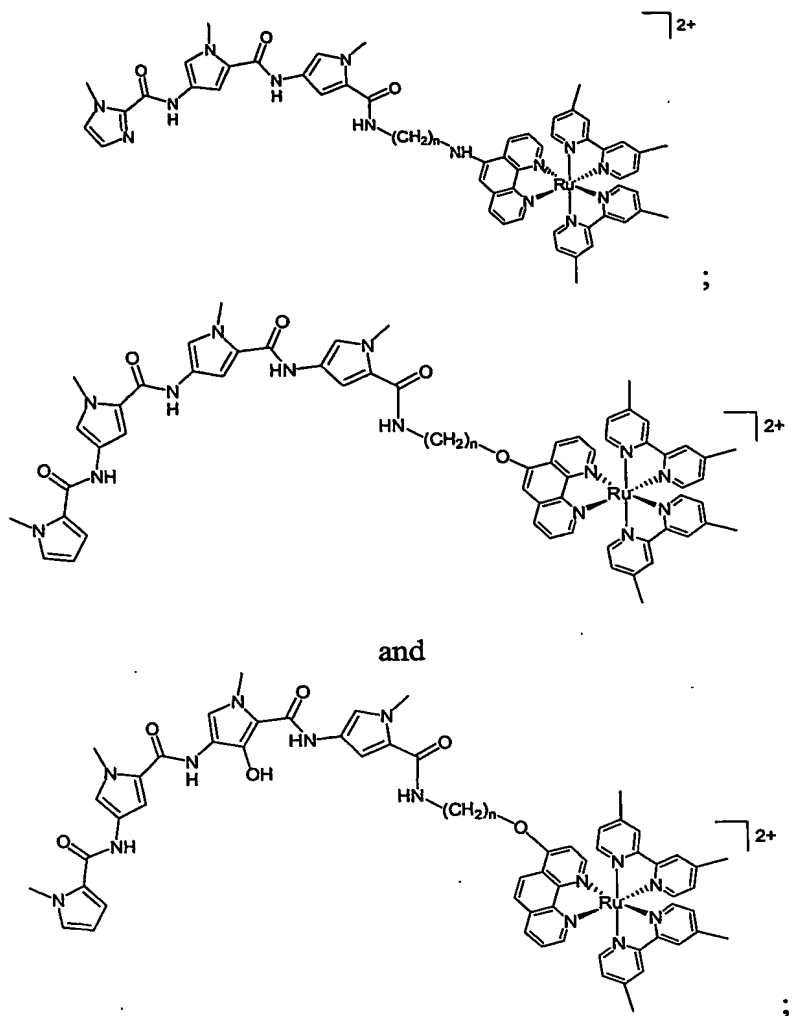
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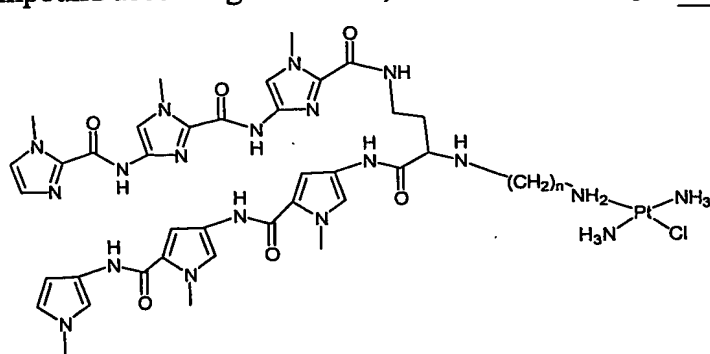
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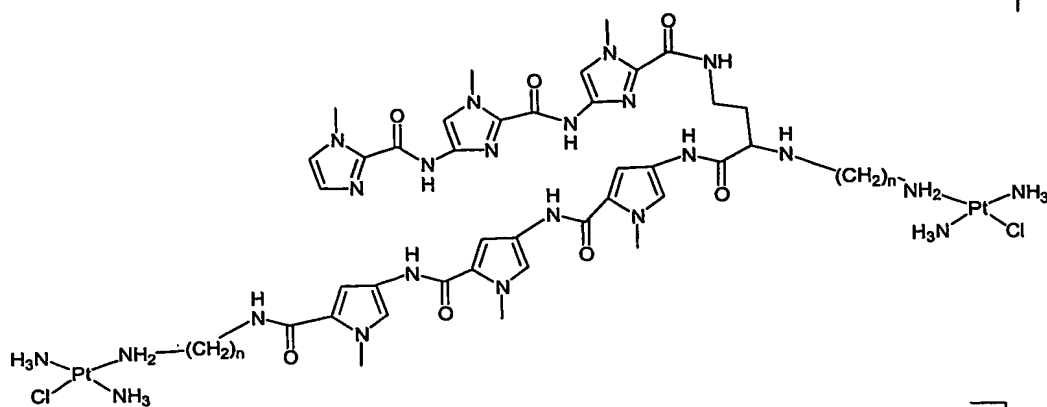
5 where n is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

14. A compound according to claim 9, wherein said compound is selected from

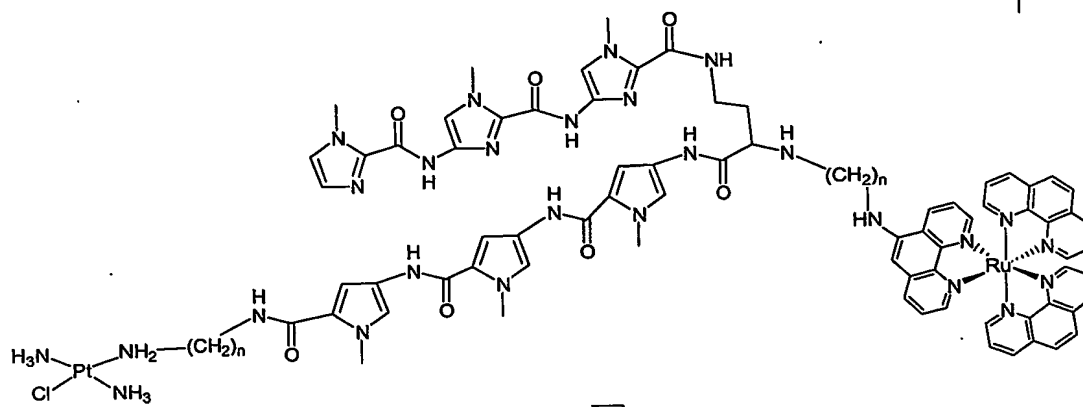


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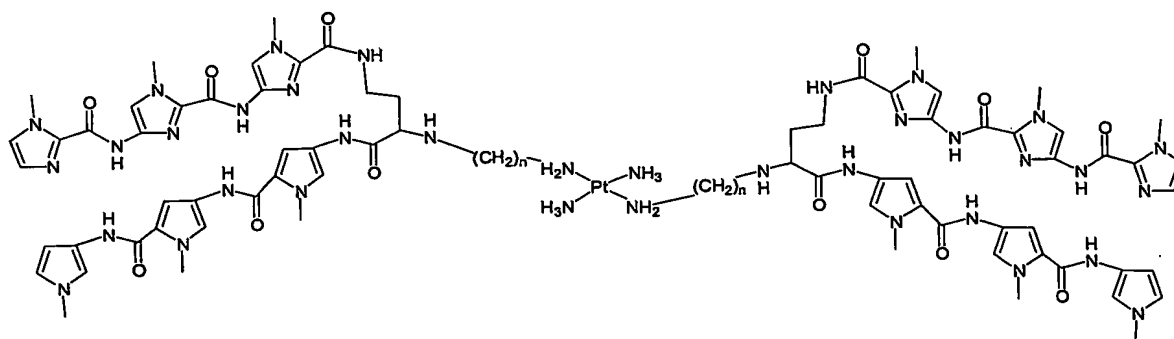
2+



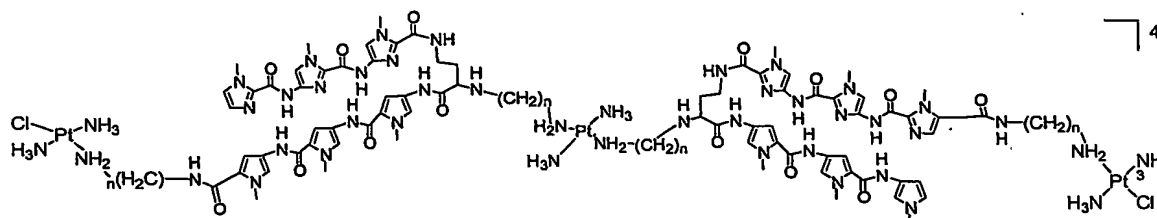
3+



1+

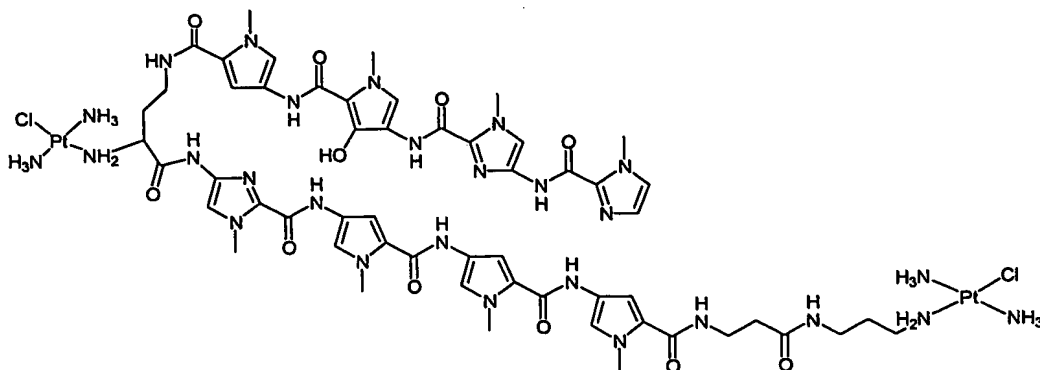


4+



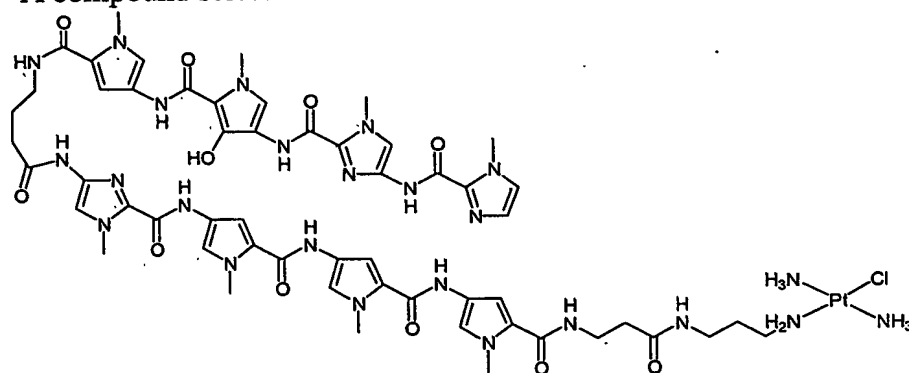
5

and

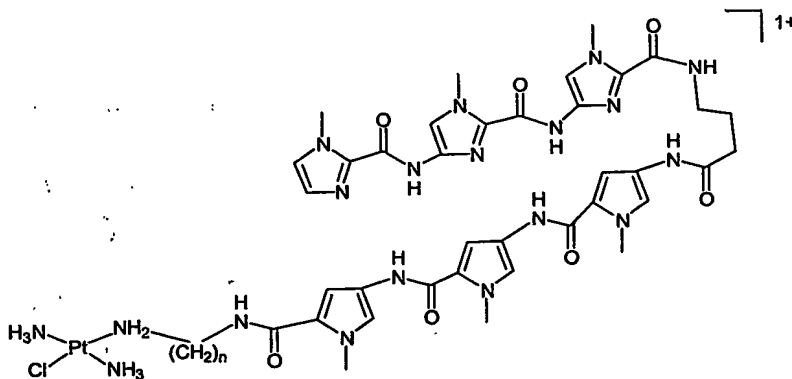


where each n is an integer independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

15. A compound selected from



and



where each n is an integer independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

16. A pharmaceutical composition comprising at least one compound selected from a compound of formula (1) according claim 1, a compound of formula (3) according to claim 9, and a compound according to claim 15, together with a pharmaceutically acceptable diluent, adjuvant or carrier.

17. A method of targeting a therapeutic agent(s) and/or a reporter group(s) to a sequence in a polynucleotide comprising contacting biological material suspected of containing said sequence with a compound of formula (1), formula (3) or claim 15.

18. A method of treating a disease selected from cancer, HIV and Hepatitis C, said method comprising administering to a mammal in need of such treatment a therapeutically effective amount of at least one compound according to claim 1, claim 9 or claim 15, or a pharmaceutical composition according to claim 16.

19. A method of diagnosis comprising contacting a biological sample with a diagnostically effective amount of at least one compound according to claim 1, claim 9 or claim 15, or a pharmaceutical composition according to claim 16.

Dated 22 December, 2005
University of Western Sydney

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Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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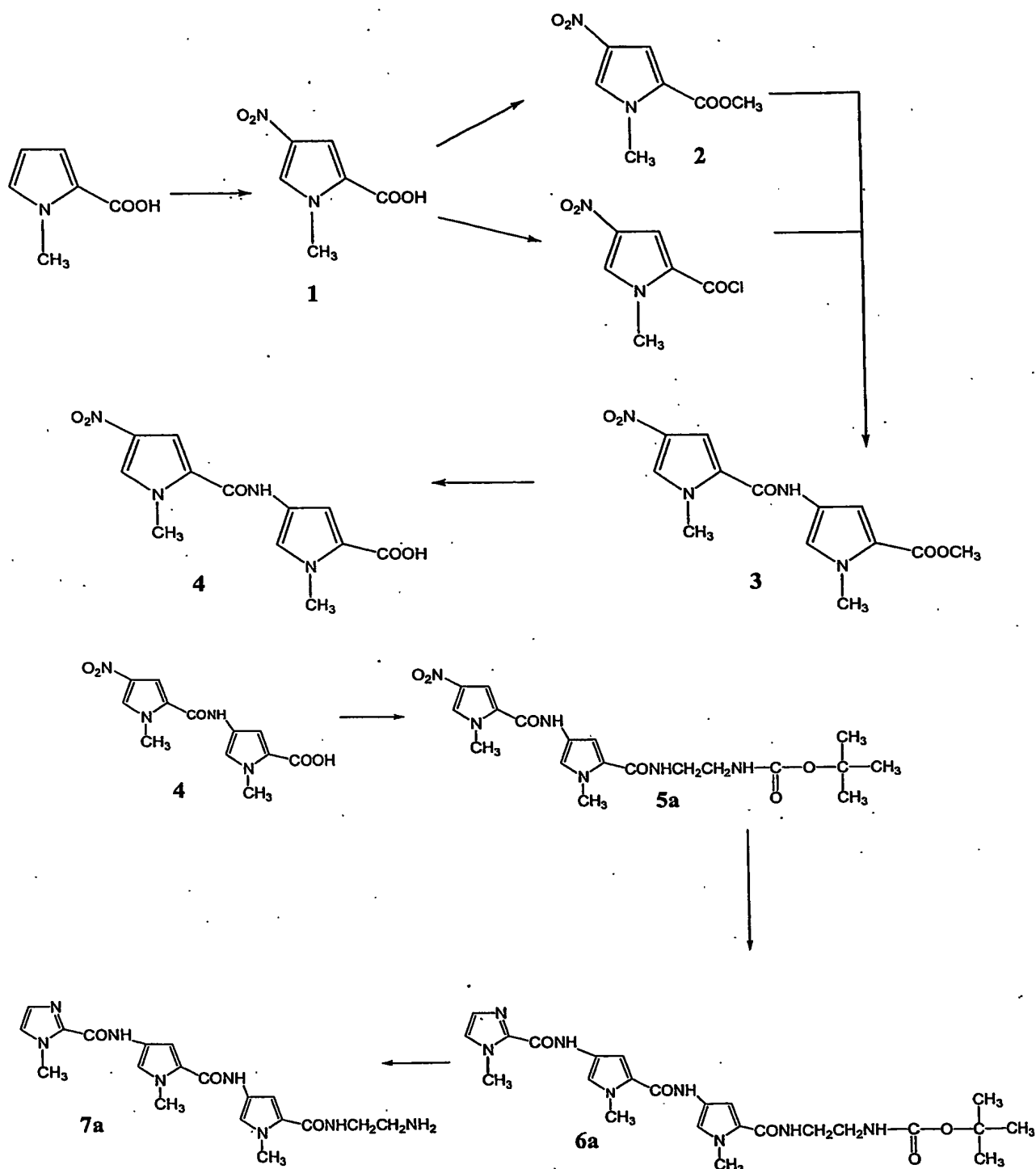


Figure 1

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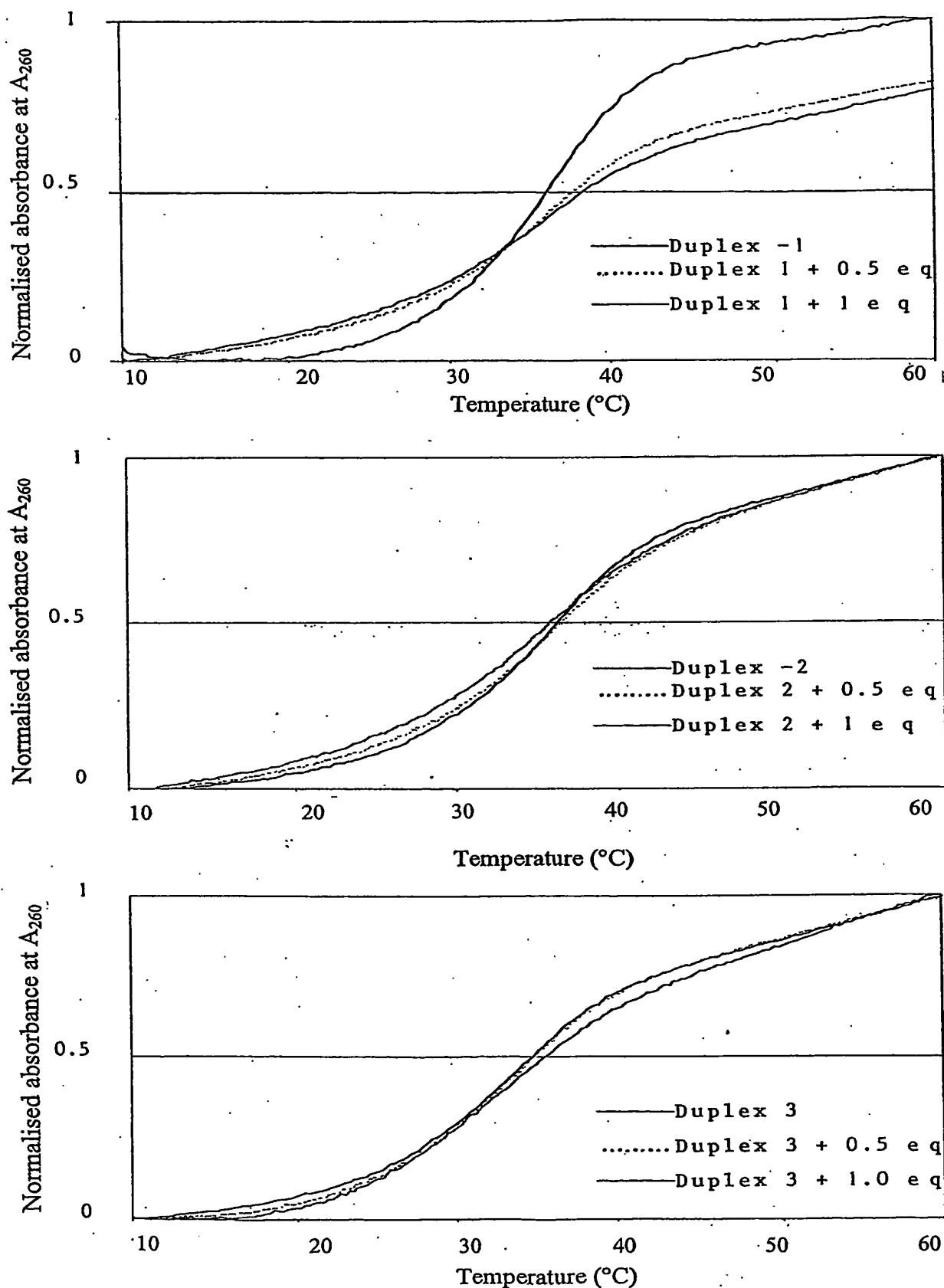


Figure 2

CD titration Spectra

ICD titration Spectra

DJ1953-2 trans-lm/Py/Py-[CONH(CH₂)₂-NH₂)Pt(NH₃)₂Cl

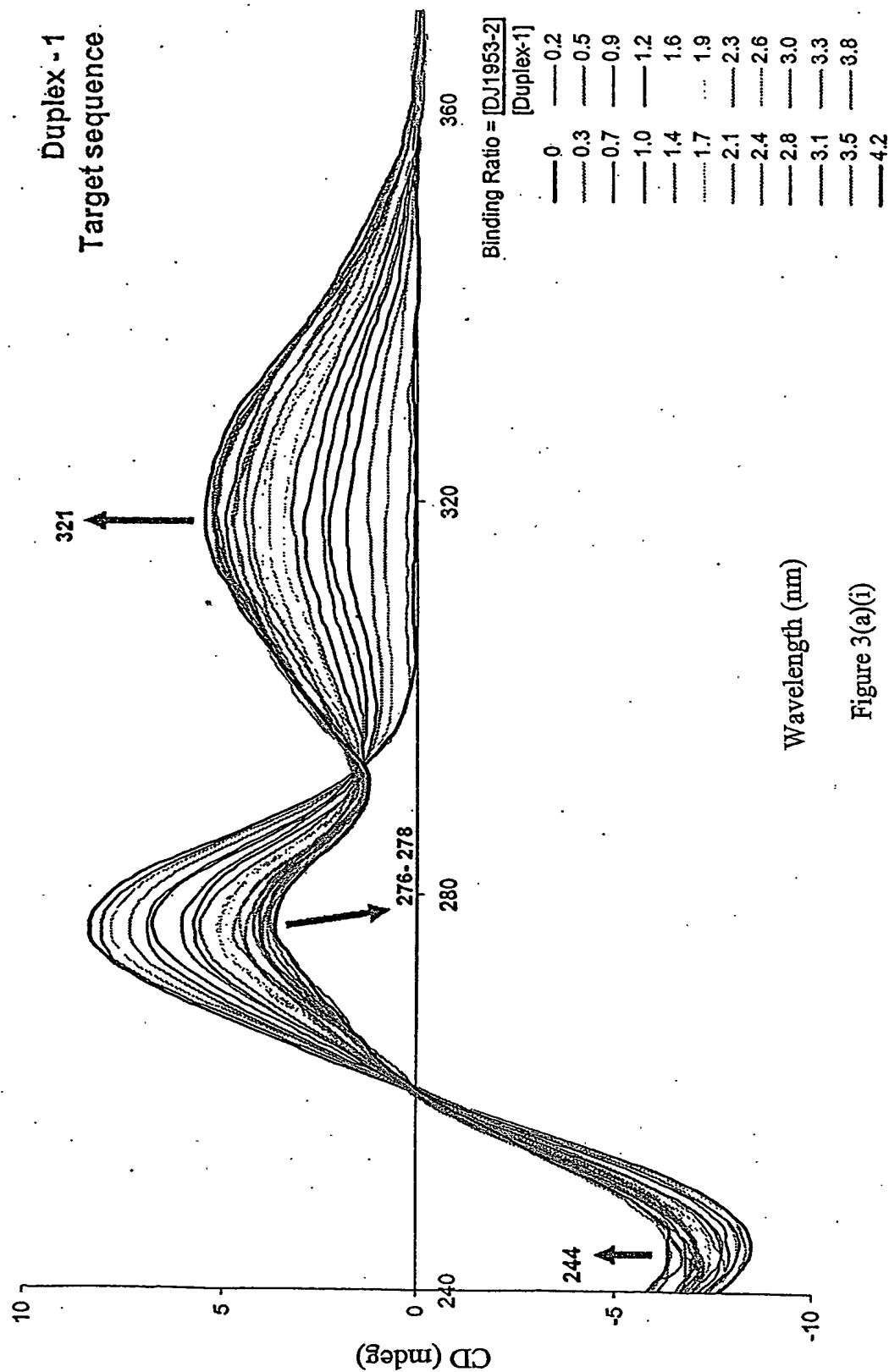


Figure 3(a)(i)

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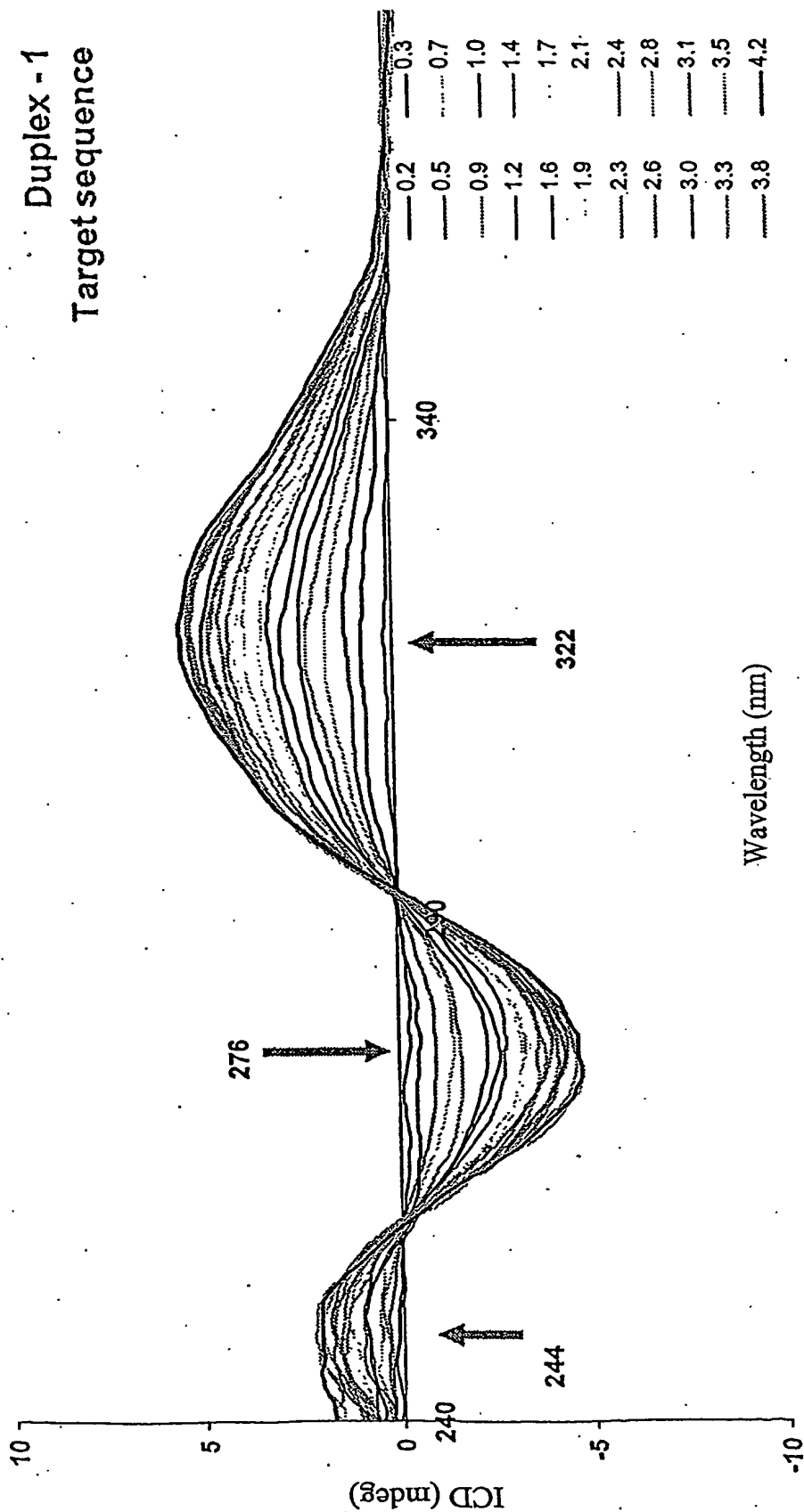


Figure 3(a)(ii)

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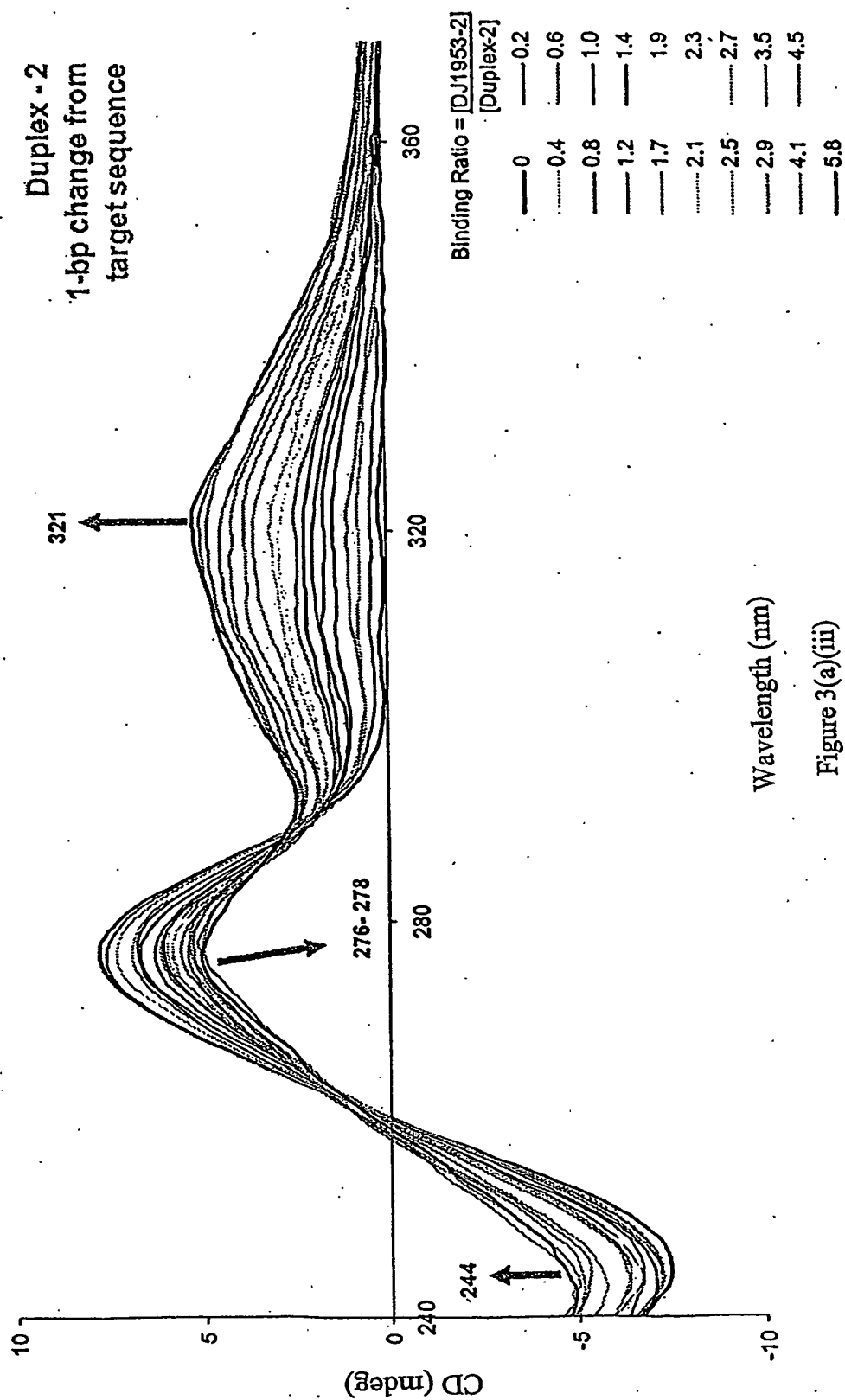
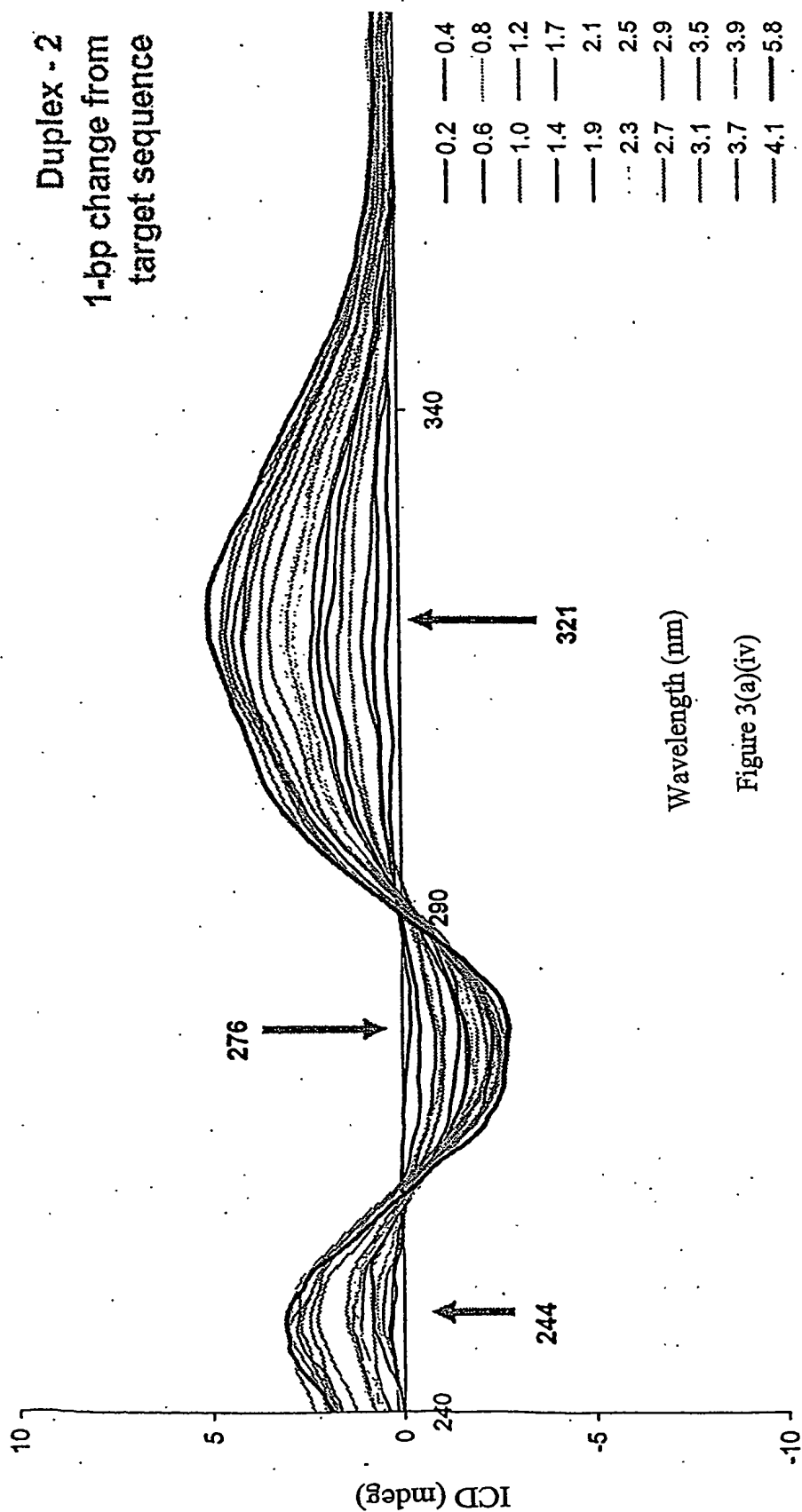


Figure 3(a)(iii)

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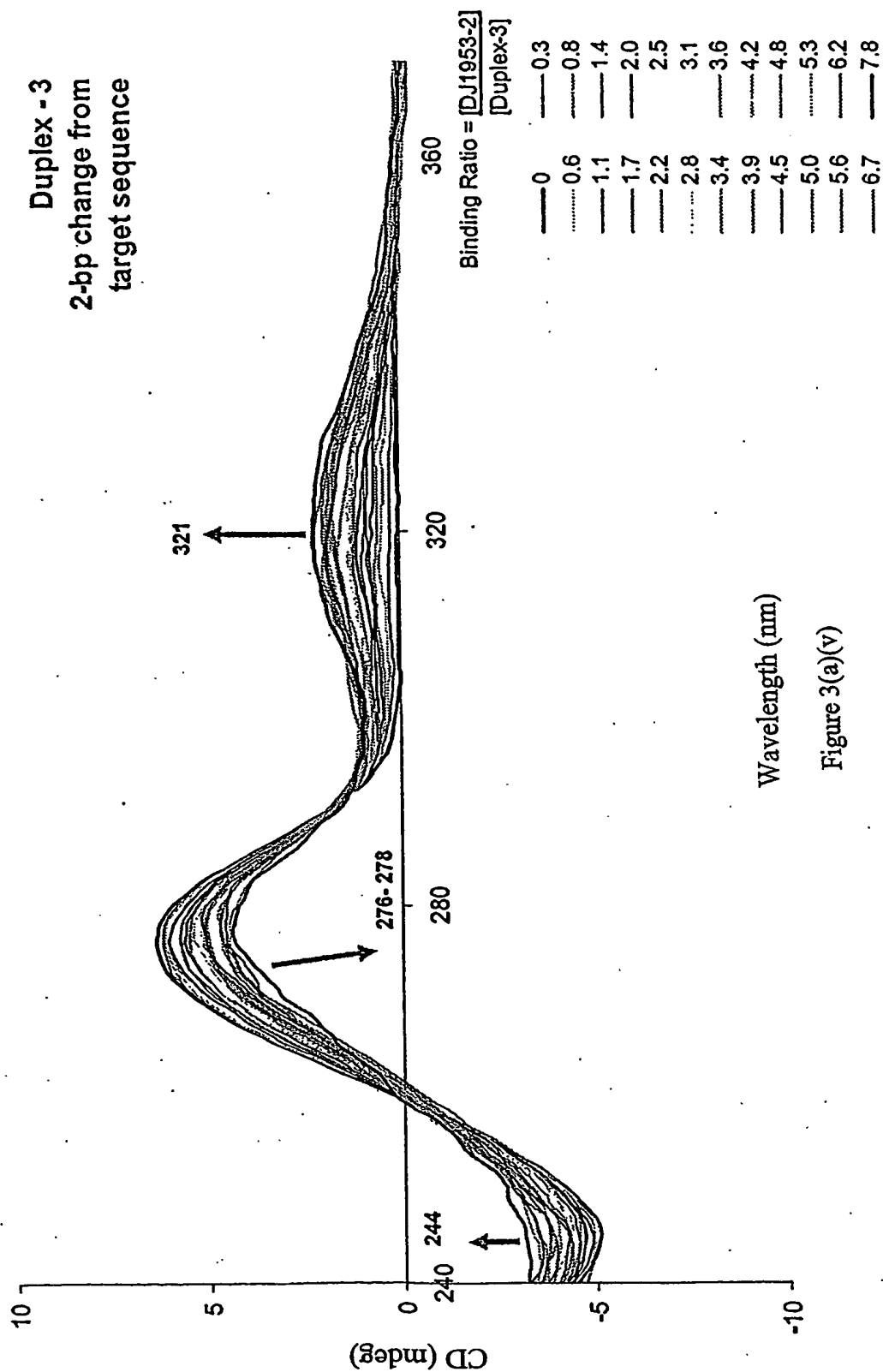
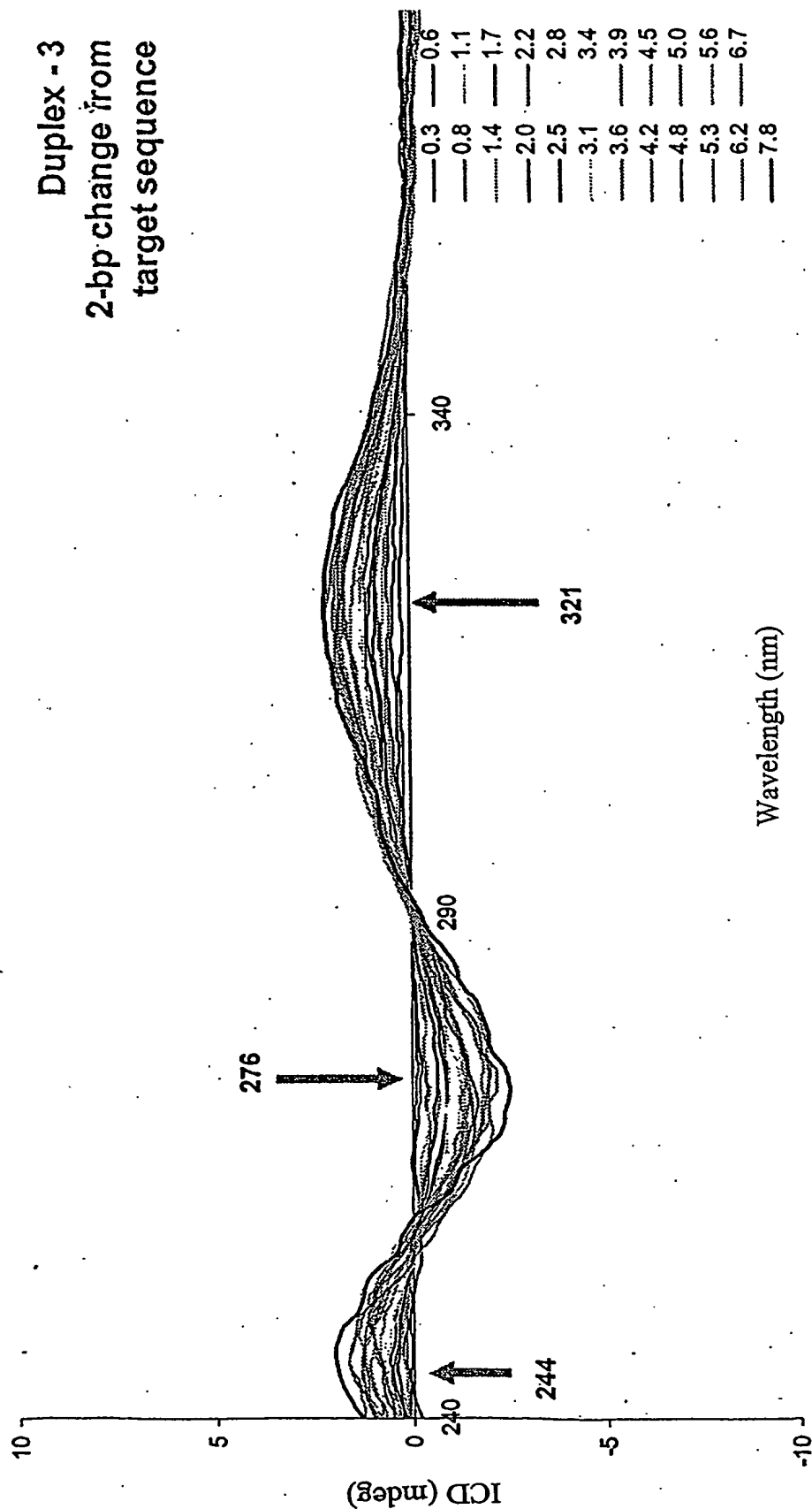


Figure 3(a)(v)

Duplex - 3
2-bp change from
target sequence



Wavelength (nm)

Figure 3(a)(vi)

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trans-Im/Py/Py-[CONH(CH₂)₆-NH₂)Pt(NH₃)₂Cl

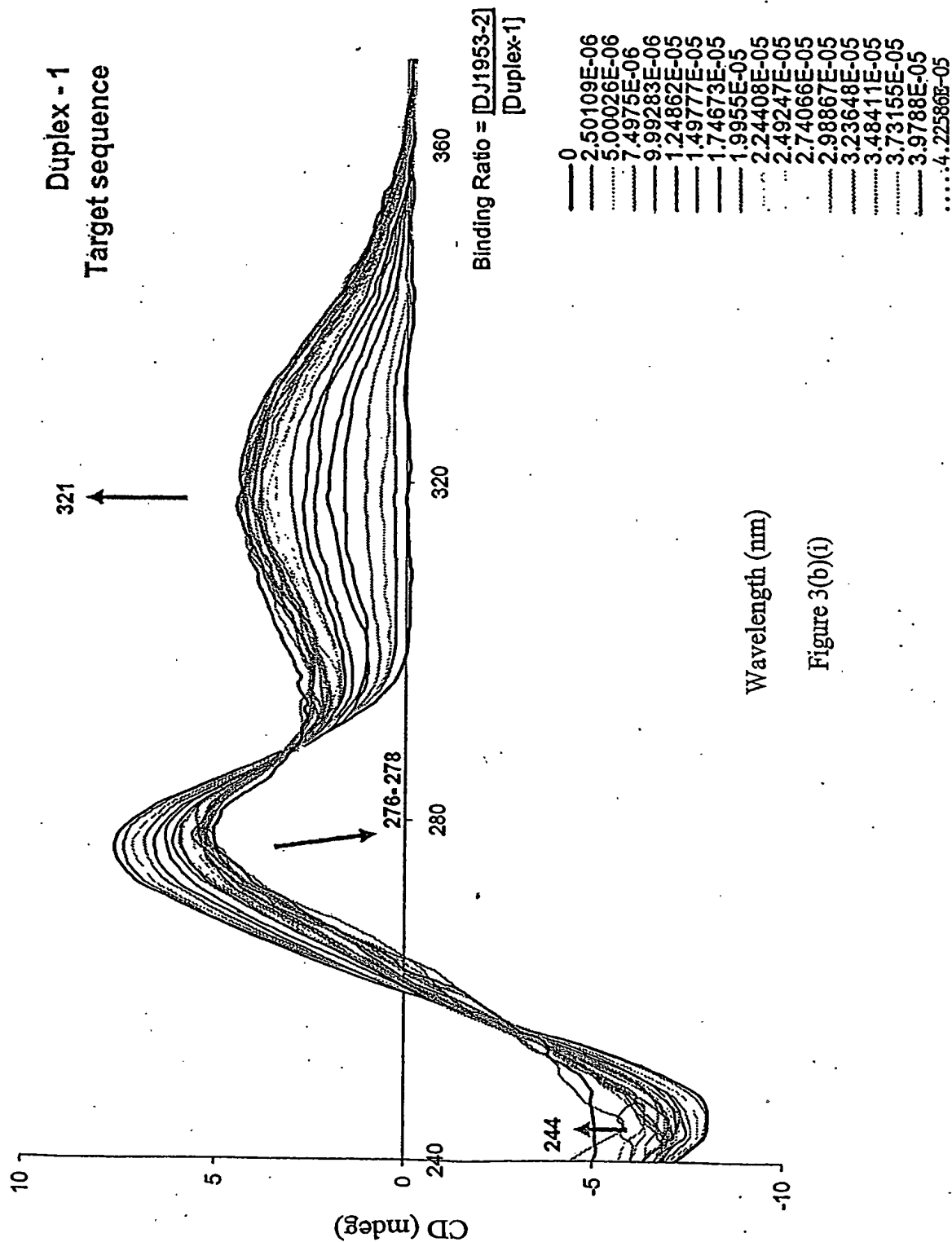


Figure 3(b)(i)

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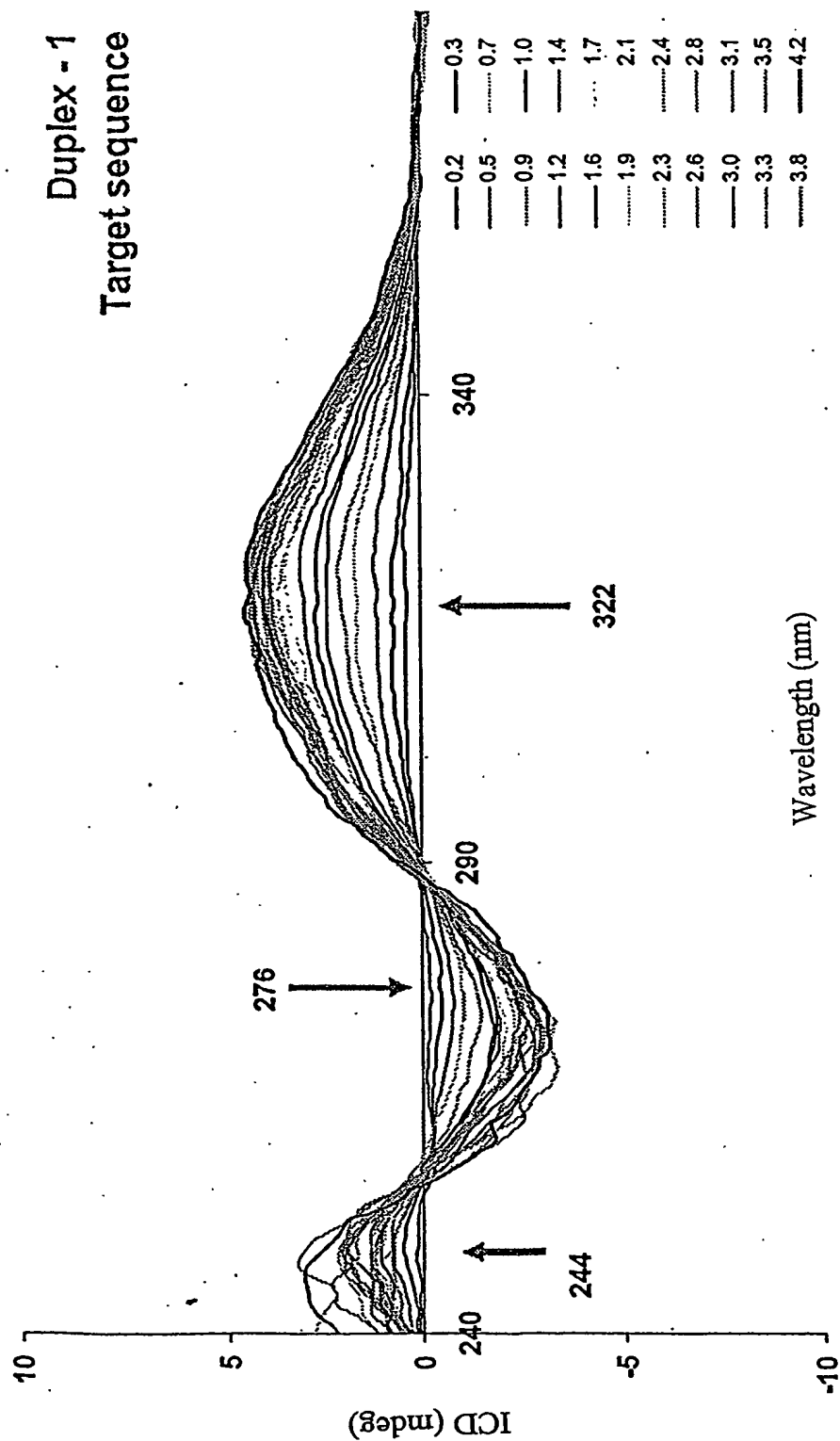


Figure 3(b)(ii)

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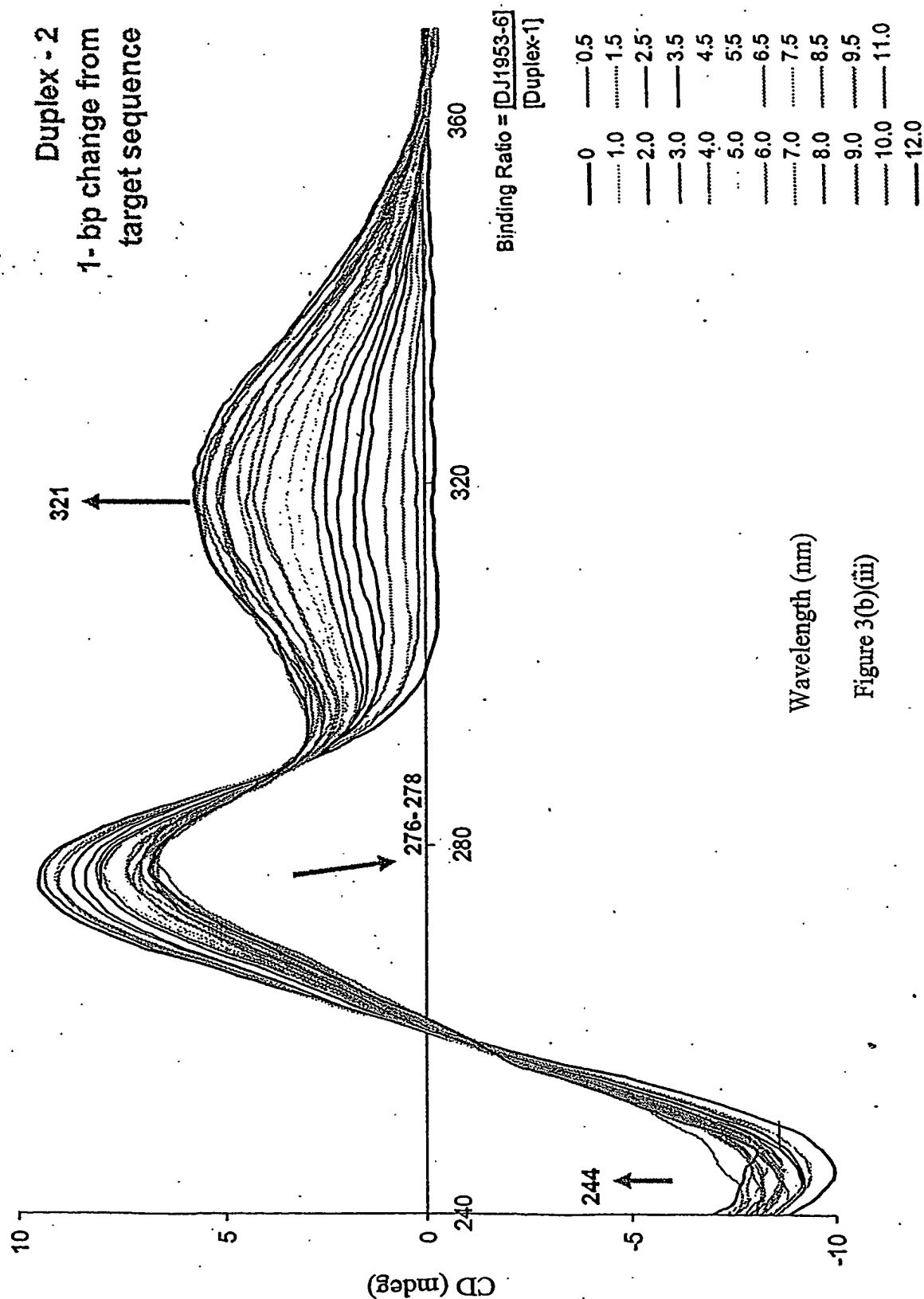


Figure 3(b)(iii)

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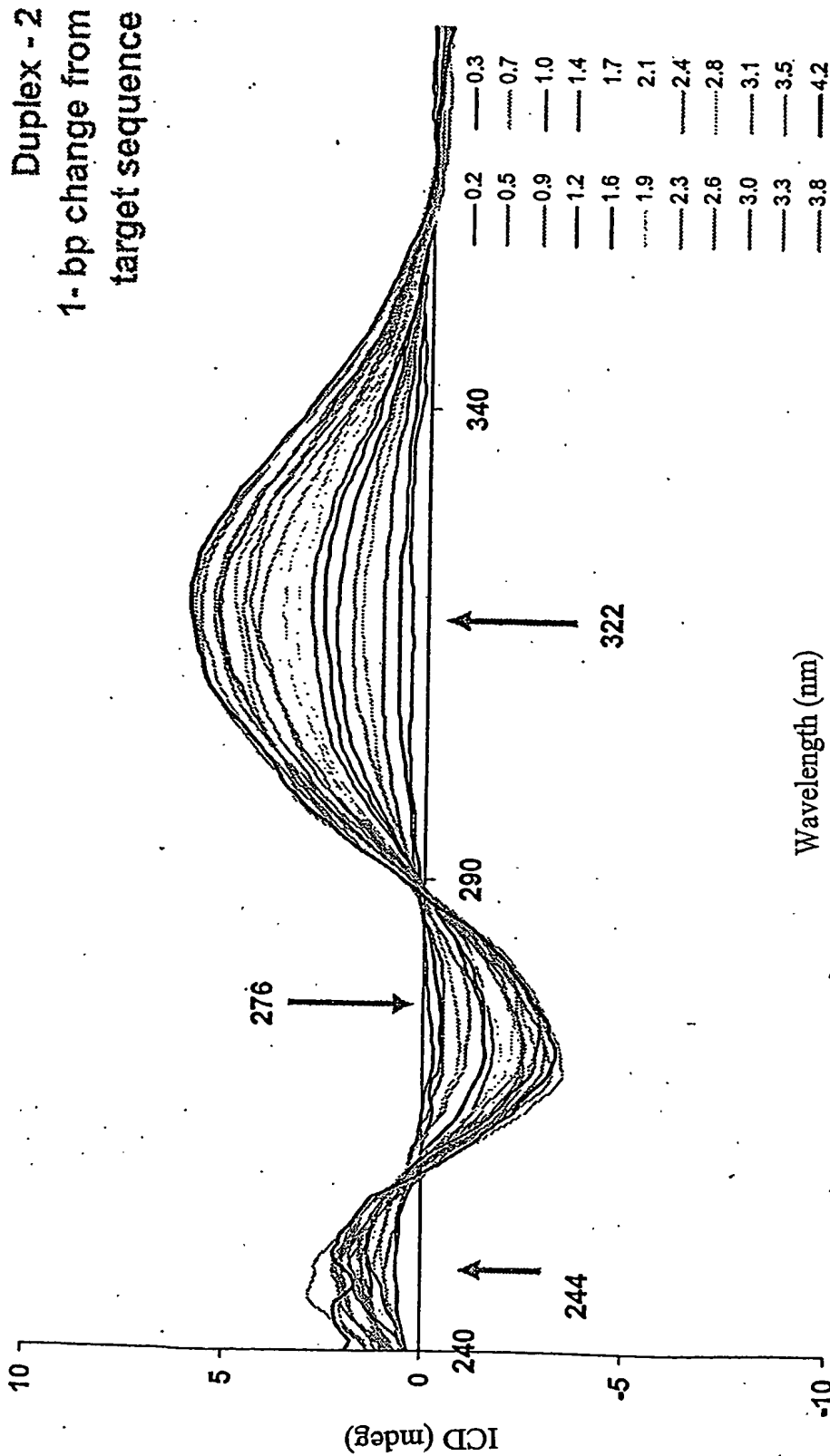
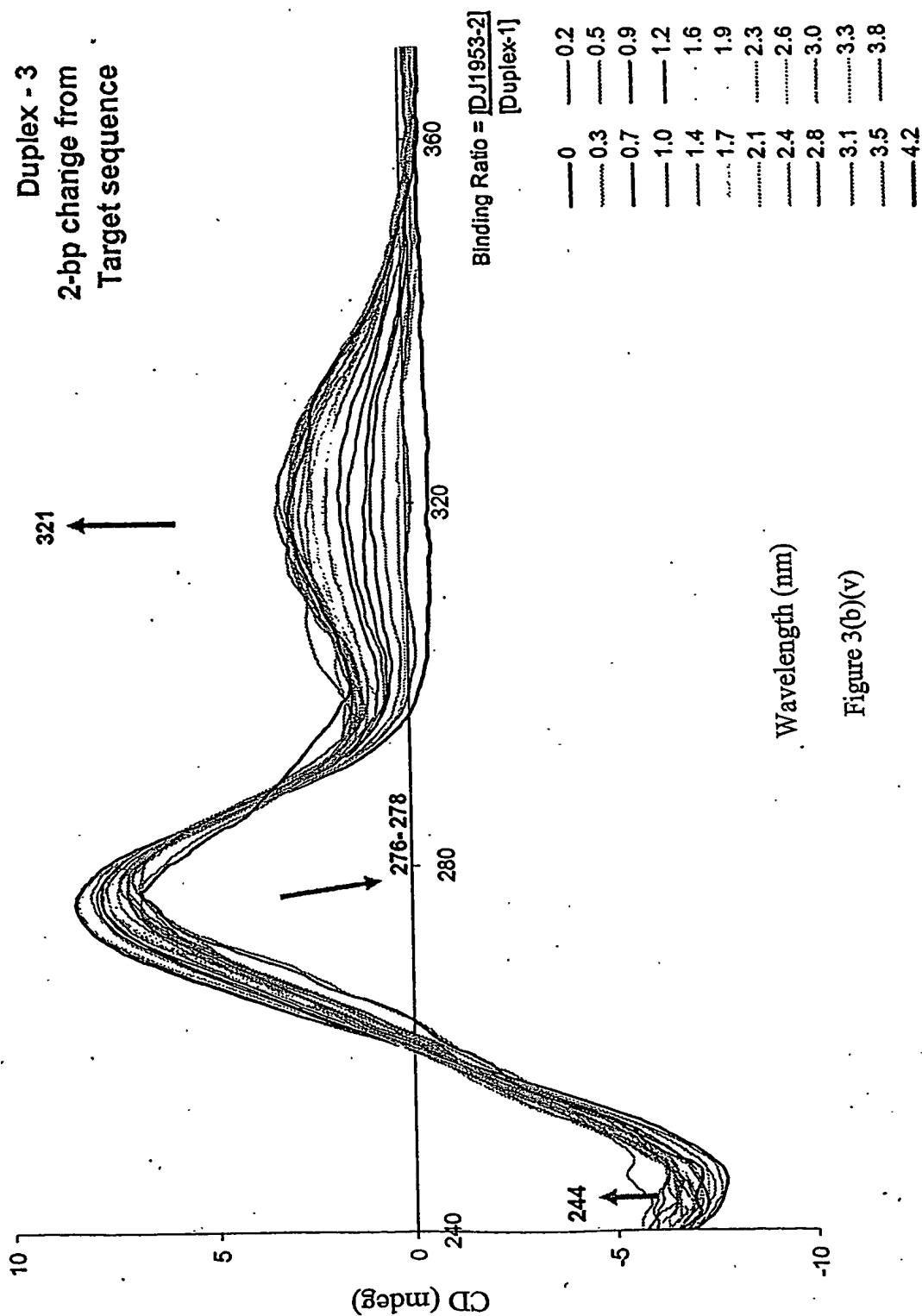


Figure 3(b)(iv)



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Duplex - 3
2-bp change from
Target sequence

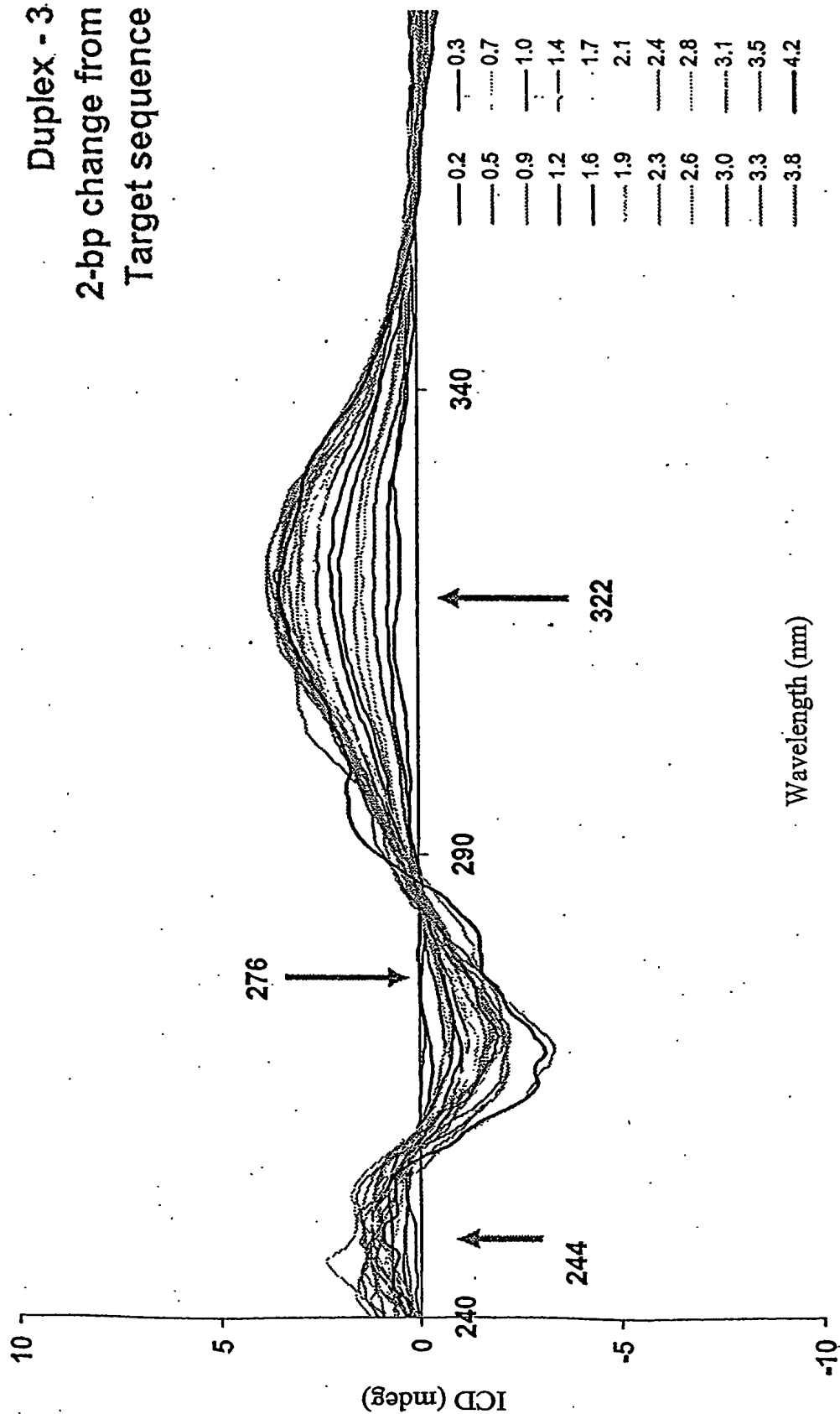


Figure 3(b)(vi)

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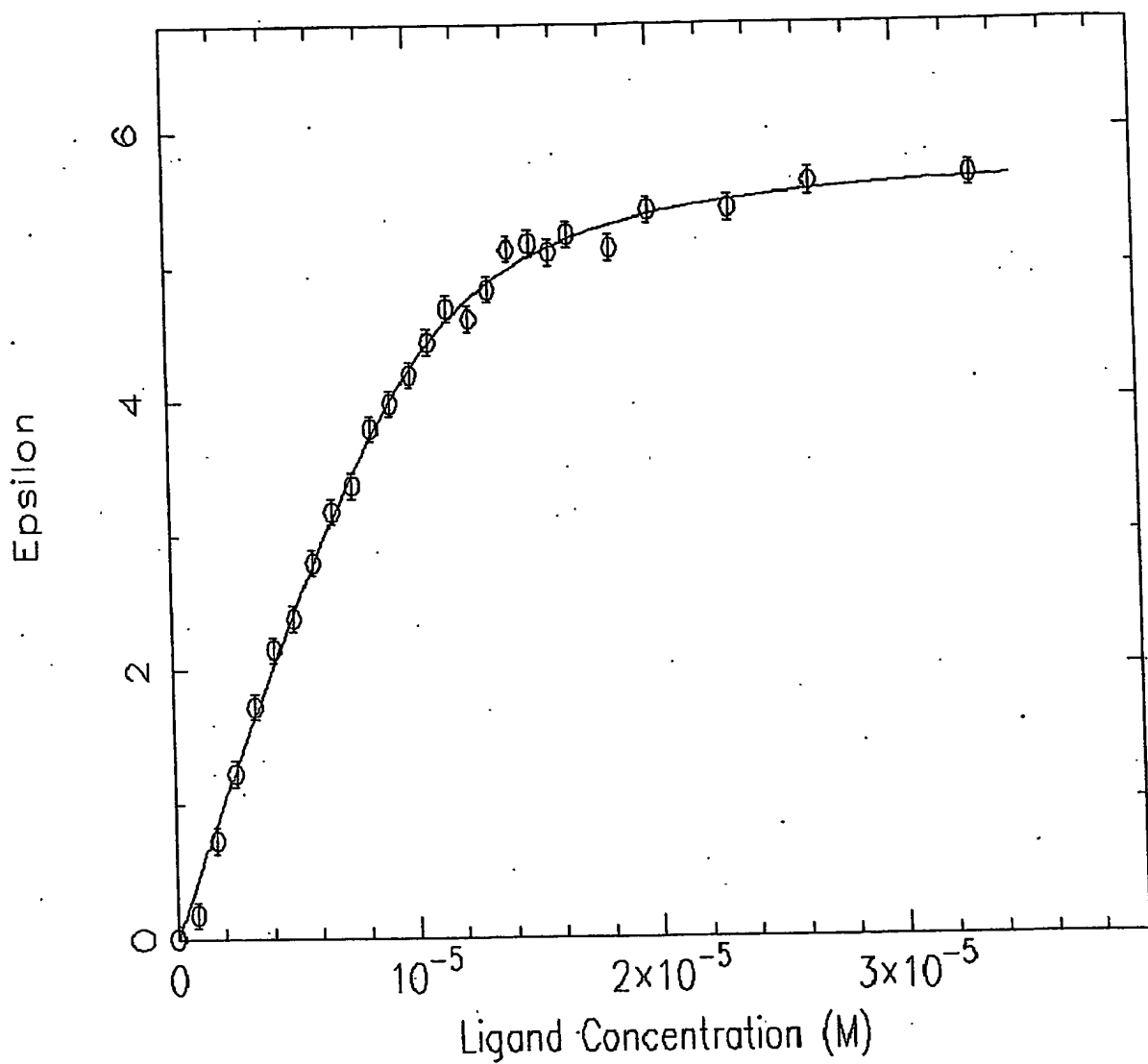


Figure 3c

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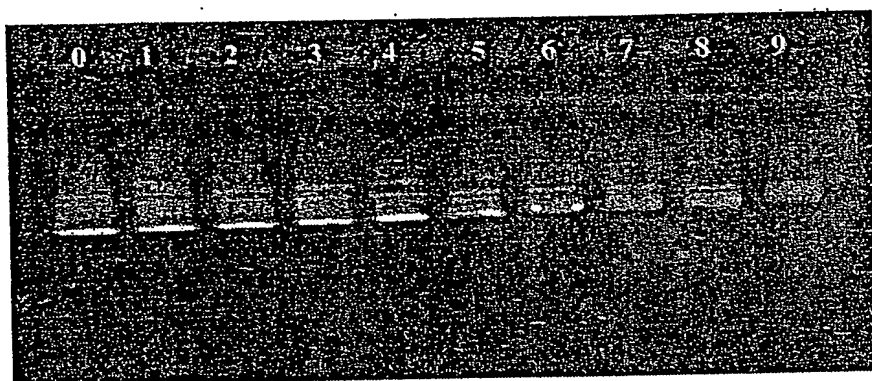


Figure 4

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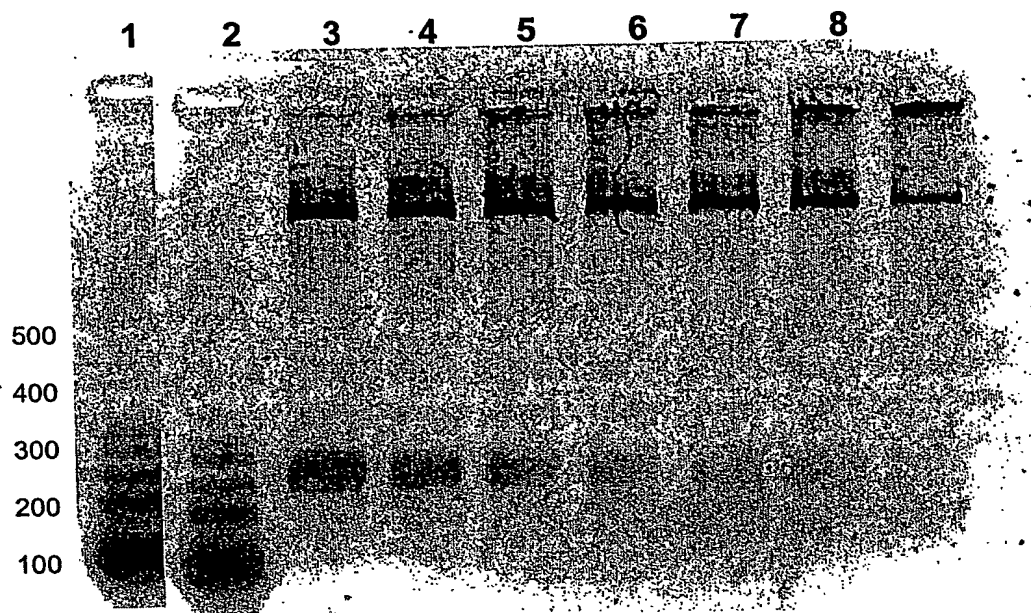


Figure 5.

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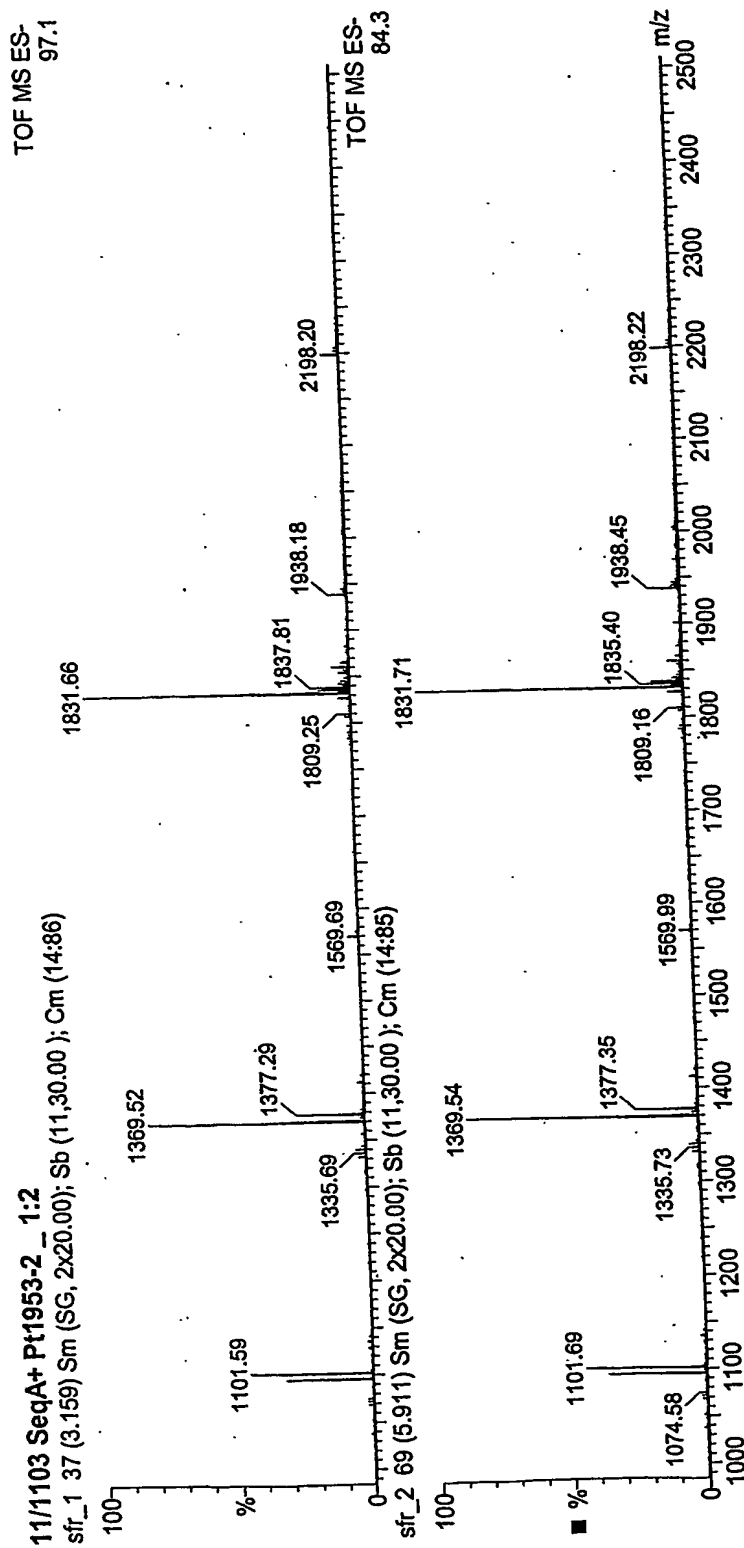


Figure 6

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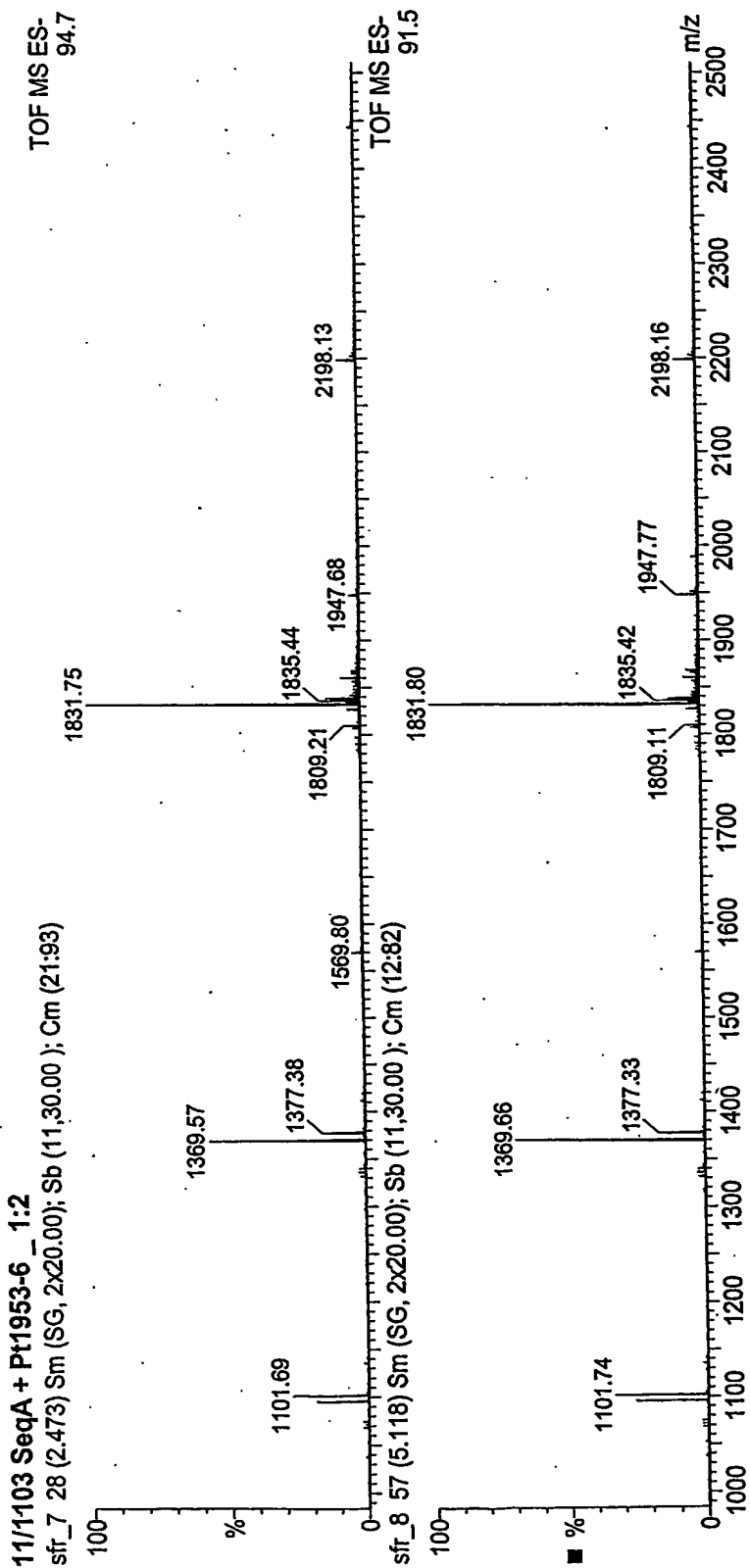


Figure 7

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